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Abstract Growth failure is a well-known problem in infants with bronchopulmonary dysplasia (BPD). We studied BPD infants' total daily energy expenditure (Ee), nutritional balance, and growth in relation to their past and current clinical status. Applying the doubly labelled water technique, Ee was measured in nine preterm infants with BPD receiving supplemental oxygen (postnatal age 61 ± 13 days) and nine matched controls (36 ± 21 days) during a 6-day period. Energy and protein balance, past and present respiratory status, and growth were assessed as well. The results show that Ee was higher in the BPD infants compared to controls (73 ± 9 vs 63 ± 8 kcal/kg/day, $P < 0.05$), but their faecal energy loss was lower ($P < 0.01$). Weight gain, energy intake, energy cost of growth, protein retention, and physical activity were not different. The respiratory frequency (RR) in the BPD infants was elevated in comparison with controls ($P < 0.01$). Within the BPD group, RR was positively correlated with energy expenditure (regression equation: Ee [kcal/kg/day] = 26.3 + 0.71*RR [min^{-1}]; $r^2 = 0.82$, $P < 0.001$), and was the single most significant determinant of Ee.

Conclusion Total energy expenditure in BPD infants is elevated and is strongly associated with their respiratory status. These findings could be of practical value for the nutritional management in infants with severe BPD.

Key words Preterm infant · Bronchopulmonary dysplasia · Energy expenditure · Growth · Corticosteroids

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Abbreviations *BPD* bronchopulmonary dysplasia · *Ee* total daily energy expenditure · F_iO_2 inspiratory fraction of oxygen · *RR* respiratory frequency

Introduction

Growth failure is a well-known problem in infants with bronchopulmonary dysplasia (BPD) [1, 14, 22] but its determinants have not yet been fully elucidated. Disturbances in energy balance have been implicated with growth failure in BPD infants. Several controlled studies have demonstrated increased energy expenditure in infants with BPD [4, 11, 12, 19, 21] and a lower energy intake has been described in some of these studies. The application of the method of respiratory gas exchange, which was used to measure oxygen consumption and carbon dioxide production in these studies (in order to calculate energy expenditure), has been criticized [9]. Accurate measurements of oxygen consumption and carbon dioxide production require that the inspiratory oxygen fraction (F_1O_2) and flow of supplemental oxygen are kept constant, which is very difficult to achieve in BPD infants receiving supplemental oxygen.

The aim of the present study was to measure energy expenditure of infants with BPD and controls, applying the doubly labelled water technique which has the advantage of measuring total daily energy expenditure (Ee) over a period of days and is independent of oxygen supplementation. We also studied the relation between energy expenditure, weight gain, and clinical parameters, taking into account aspects of nutrient balance as well as past and present respiratory status in patients with mild and severe symptoms of BPD.

Patients and methods

Subjects

Assuming a significance level of 0.05 with a power of 80%, it was calculated from previous results in premature infants [20] that a

Table 1 Neonatal clinical features of BPD patients and controls

	BPD infants[a]	Control infants
Duration of pregnancy [weeks]	29.1 ± 1.4 (range 27–31)	29.8 ± 1.7 (range 27–32)
Male/female	9/0	5/4
Birth weight [g]	1106 ± 303	1206 ± 362
Apgar score:		
-at 1 min	5.3 ± 2.6	5.1 ± 2.7
-at 5 min	7.3 ± 2.0	8.1 ± 1.1
Neonatal respiratory distress:		
-Severity score (Palta et al.)	65 ± 14	–[b]

Mean ± SD.
[a] None of the BPD infants had primary heart disease or initial lung disease other than surfactant deficiency.
[b] No, or only minimal respiratory distress during the first three days of life.

minimal group size of eight infants in each group was required to measure an inter-group difference in Ee of 15%. We studied nine preterm infants with BPD and nine control infants (Table 1). The infants were matched for birth weight and gestational age. The control infants had had no or only mild, transient respiratory distress (supplemental oxygen less than 3 days postpartum), and showed no signs of respiratory distress at the time of the study. Infants with BPD were enrolled according to the Bancalari et al. [2] criteria. These infants had had moderate to severe respiratory distress after birth that required mechanical ventilation for 12–28 days. Eight BPD infants received exogenous surfactant. Severity of neonatal respiratory distress was scored according to Palta et al. [15]. At the time of the study the BPD infants had had their endotracheal tubes removed. All showed signs of respiratory distress, and they still received oxygen therapy. All had received corticosteroid therapy: hydrocortisone therapy was started in the 4th or 5th postnatal week at an initial dose of 5 mg/kg per day, and subsequently tapered in 4 weeks. In three infants a second corticosteroid course was given because severe respiratory distress recurred during tapering. At the time of the study eight BPD infants received hydrocortisone (mean dose 3 mg/kg/day); they were also treated with diuretics. The infants were maintained in a temperature-controlled neonatology ward (average temperature 29°C), and nursed in an incubator or in bed (if body weight > 2 kg).

The study was approved by the scientific and medical ethical committee of our hospital. Consent for the study was obtained in each case.

Nutrition

All patients were fed through a nasogastric tube with standard formulas (Nenatal [Nutricia, 80 kcal and 2.1 g protein/100 ml] or Nutrilon Premium [Nutricia, 67 kcal and 1.5 g protein/100 ml]. Fluid intake was prescribed individually, taking into account the respiratory and cardiac status of the infant. According to judgement of the attending physician, the formula was fortified with supplemental formula powder, glucose polymers (Caloreen, Clintec) or soya fat emulsion (Nutricia). Food quotients, calculated from formula mixtures, were no different between the patient and control groups. Food intake was kept constant during, and 2 days in advance of, the study period.

Methods

From days 1 to 6 total daily Ee was measured with the doubly labeled water technique as previously described [20]. Briefly, isotopes (0.25 g $H_2{}^{18}O$ and 0.13 g ^2H_2O per kg) were administered through a nasogastric tube, urine samples were collected daily, and isotope enrichment was measured by isotope ratio mass spectrometry. Water turnover and Ee were calculated from isotope disappearance [20], assuming a respiratory quotient of 0.89 in both groups of infants [8].

Heart rate, respiratory frequency (RR), and transcutaneous oxygen saturation were monitored continuously (Hewlett Packard, and Nellcor Instruments, USA), and recorded every hour. On day 4, physical activity was monitored during 1 min at 30-min intervals with the visual observation scale described by Freymond et al. [5]. From days 4 to 6 a balance study was performed. Nutritional intake was measured as previously described [18]. Urine was collected with self-adhesive bags during 24 h, divided into four collection periods of 6 h. Urine bags were emptied at nursing times, the urine was transposed with syringes into plastic containers kept at 4°C until the end of each period, and then frozen at −20°C until analysis. Urine that leaked from the collection bag was collected in diapers that were weighed before and after each nursing period; urinary nitrogen excretion was corrected for these losses. Urine collection was complete for > 90% of total urine output in all but one patient. During 72 h, the faeces was collected in the diapers with fat-free paper which retained the faeces but not the urine. Faecal specimens were transposed into plastic containers and frozen as described above. Calculations of faecal energy and nitrogen loss were corrected for faeces retained in the collection paper. Faecal collections were approximately > 90% complete. Energy stored was calculated from energy intake minus faecal energy loss minus Ee (Urinary energy loss is very small and was neglected in the calculations). Nitrogen intake and nitrogen loss (in 72 h faeces collections, as well as in 24 h urine collected on day 4) were measured with a standard technique (modified Micro-Kjeldahl method) [13]. Protein balance was calculated assuming that 1g of nitrogen represents 6.25 g of protein.

Growth rates were assessed from anthropometry performed on days 1 and 6, assuming linear growth. Body weight was measured with an electronic scale (Seca, Germany) with an accuracy of 5g. Measurements of skeletal growth (crown-heel length, crown-rump length, and arm span) were made with the infant in the supine position, using a measuring device resembling the Harpenden infantometer [6]. Head circumference was measured as described by Gerver et al. [7].

All measurements were normally distributed, and are reported as mean ± SD unless otherwise stated. Statistical comparisons were made with unpaired *t* tests. Simple and multiple regression analyses were also conducted. Statistical differences were considered significant if $P < 0.05$ (two-tailed).

Results

Infants in both groups had similar Apgar scores, but differences existed in gender distribution, and postnatal and post-conceptual age (Tables 1, 2).

Nutritional balance and growth

Table 3 shows the results of the balance studies. Fluid intake and water turnover were significantly lower in the BPD infants than in controls. Energy intake in both

Table 2 Features of BPD patients and controls during the study period

		BPD infants	Control infants
Start study protocol:			
-postnatal days		61* ± 14	36 ± 21
-post-conceptual weeks		38** ± 2	34 ± 3
F_iO_2 (range)	[l/l]	0.23 – 0.55	Room air
Oxygen saturation	[%]	92 ± 2	NA
Respiration rate	[min^{-1}]	65* ± 12	50 ± 6
Heart rate	[min^{-1}]	158 ± 8	153 ± 9
Physical activity	[Freymond score]	0.66 ± 0.20	0.62 ± 0.05
Body weight	[g]	2000 ± 492	1752 ± 454
Total body water	[% body weight]	73** ± 6	80 ± 4
Crown heel length	[*10^{-1} m]	43.1 ± 3.7	42.4 ± 3.1
Head circumference	[*10^{-1} m]	31.0 ± 2.4	30.0 ± 2.2

Mean ± SD
NA Not available. Significant difference to controls (*t* test): *$P < 0.01$, **$P < 0.05$.

Table 3 Nutritional balance studies and growth rates

		BPD infants	Control infants
Water	[ml/kg/day]:		
-fluid intake		117* ± 6	156 ± 14
-water turnover		132** ± 12	161 ± 20
Energy	[kcal/kg/day]:		
-intake (Ei)		119 ± 16	117 ± 8
-faecal loss (El)		6* ± 3	14 ± 8
-total energy expenditure	(Ee)	73*** ± 9	63[b] ± 8
-energy stored (Es)		40 ± 13	40 ± 13
Protein	[g/kg/day]:		
-intake		2.93 ± 0.21	3.05 ± 27
-faecal loss		0.13** ± 0.07	0.38 ± 0.16
-urine loss		0.72 ± 0.41	0.54 ± 0.29
-protein retention		2.08 ± 0.46	2.13 ± 44
Growth rates:			
Body weight	[g/kg/day]	12.9 ± 5.4	12.6 ± 3.5
Skeletal growth[a]	[mm/m/day]	1.9*** ± 2.7	3.5 ± 2.5
Head circumference	[mm/m/day]	1.8 ± 4.2	3.9 ± 3.4

Mean ± SD.
Significant difference with controls (*t* test): ***$P < 0.05$, *$P < 0.01$, **$P < 0.001$.
[a] Arithmic mean of crown-heel length, crown-rump length, and arm span. In a principal components analysis, these parameters formed one factor (Eigenvalue 1.47, percentage of variance: 49%).
[b] Male and female controls: 60 ± 8 and 66 ± 8 kcal/kg/day, respectively (*t* test: NS).

groups was similar but faecal energy loss was significantly lower in the BPD infants than in controls ($P < 0.001$). Mean Ee was 16% higher in the BPD infants than in the control infants (73 vs 63 kcal/kg/day [303 vs 262 kJ/kg/day], $P = 0.03$). All infants had a positive energy balance during the study. As a result, energy stored was not significantly different between both groups. Within the BPD group energy stored was significantly associated with energy intake ($r^2 = 0.78$, $P < 0.01$), but not with Ee ($r^2 = 0.09$, NS).

Both groups of infants had similar values for anthropometric parameters (Table 2), but total body water was significantly higher in the controls than in the BPD infants ($P < 0.05$). Weight gain and energy cost of growth were very similar in both groups (12.9 ± 5.4 g/kg/day and 3.5 ± 1.4 kcal/g in BPD infants vs 12.6 ± 3.5 g/kg/day and 3.5 ± 1.7 kcal/g in controls (NS), respectively). As shown in Table 3, growth velocities of head circumference were not significantly different between both groups, but the mean velocity of skeletal growth was significantly lower in the BPD infants compared to controls ($P = 0.03$) . In the BPD infants, the steroid dose received during the study period was not significantly associated with growth velocities.

Clinical status and energy expenditure

Physical activity score and heart rate were similar in both groups (Table 2), but RR was significantly higher in the BPD patients compared to the control infants (65 ± 12 vs 50 ± 6 breaths/min, $P = 0.005$). Mean Ee in the four BPD infants who had a RR > 62 breaths/min (i.e. above the 95th percentile of RR in the controls), was 79 kcal/kg per day (331 kJ/kg per day), that is 25% increased compared to control values. Univariate correlation analyses showed significant associations between RR ($P < 0.001$), heart rate ($P < 0.05$), and F_iO_2 ($P < 0.01$), and Ee as dependent variable ($r^2 = 0.82$, 0.69, and 0.69, respectively). In multiple regression analysis, these three factors predicted a high proportion of the variance in Ee within the group of BPD infants (multiple $r^2 = 0.94$, $P < 0.01$; regression equation: $Ee = -72 - 56.6 * F_iO_2 + 0.64 *$ heart rate $+ 0.95 *$ RR). For RR, the single most significant determinant of Ee ($r^2 = 0.82$, $P < 0.001$), the regression equation was: Ee [in kcal/kg/day] = 26.3 + 0.71 * RR [in breaths/min]). Figure 1 depicts the relationship between RR and Ee in the BPD infants; in the control infants no association between RR and Ee was present. In the BPD group, F_iO_2 at postnatal day 28 was significantly cor-

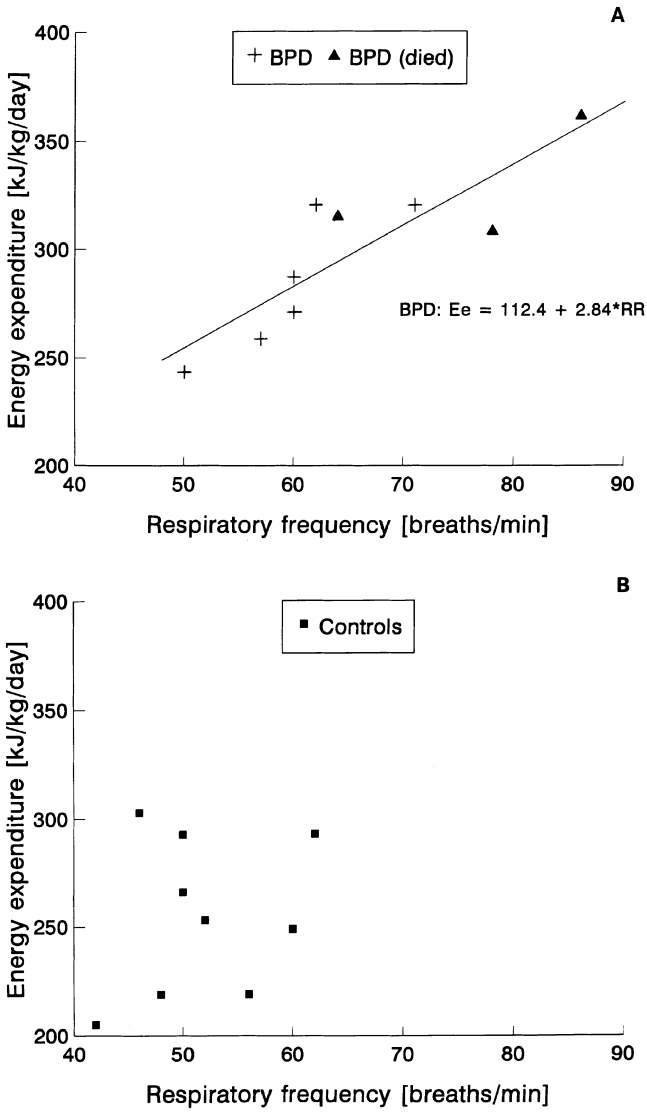

Fig. 1 Respiratory frequency and total daily energy expenditure. *Panel A*: BPD infants ($r^2 = 0.82$, $P < 0.001$). *Panel B*: Control infants ($r^2 = 0.31$, $P = 0.46$).

related with Ee ($r^2 = 0.84$, $P < 0.005$), but factors in the patient history (birth weight, days on mechanical ventilation, Palta score), and current anthropometric status, physical activity score, and steroid dose were not significantly associated with Ee.

Outcome

Three BPD infants later died due to pulmonary or cardiac insufficiency, all within the first 6 months after birth. In retrospect, respiratory status in these infants had been more serious during the study period (Fig. 1). No differences existed in energy and protein retention and growth during the study period between BPD infants who died compared to the survivors. At a corrected age of 1 year, two out of the six survivors (but none of the controls) had a supine length below the 3rd percentile of the Dutch reference population [17].

Discussion

The results of the present study indicate that total daily energy expenditure in infants with BPD is increased and that Ee in these patients is strongly associated with clinical parameters of pulmonary dysfunction (respiratory frequency and F_iO_2).

With respect to the elevated energy expenditure in BPD infants, the finding that Ee is 16% increased over control values is in close agreement with previous studies in BPD infants using respiratory calorimetry which reported an increase of approximately 25% [4, 19, 21]. However, two potential sources of bias in our study should be considered. Firstly, gender distribution was uneven in our study. According to the literature, energy expenditure in preterm and term female infants is higher than in male infants [3]. In our control group, females had a 10% higher Ee than males but the difference was not statistically significant. Secondly, postnatal age in the BPD infants was almost twice that of controls (61 vs 36 days) and this was also reflected in differences in their post-conceptual age. Finding an adequate control group was a problem in this and previous (e.g. [12]) studies of BPD infants. The Ee of healthy infants of comparable post-conceptual age as the BPD patients would be expected to be similar or even lower than in our control infants [16, 20, 22]. Gender and age bias might have obscured a real larger difference in Ee between our infants with BPD and the present control group. Nonetheless, Ee was significantly elevated in the BPD group (which included infants with F_iO_2 requirements ranging from 0.23–0.55). Differences in postnatal age might also explain the lower faecal energy and protein loss in the BPD patients compared to the controls because gut maturation and increased body fat mass are well-known correlatives of postnatal growth in preterm infants. The lower proportion of body water in the BPD patients also could be related to their maturation, however, lower fluid intake and use of diuretics in the BPD group may also be associated with their lower proportion of body water. It cannot be excluded that the above differences between the patient and control groups are the result of other confounding factors such as steroid use. Within the BPD group no significant correlations existed between water intake and dose of steroids or diuretics and Ee and faecal energy and protein loss and proportion of body water.

With respect to associations with the patients clinical status, severity of pulmonary disease, as indicated by current RR and F_iO_2, was significantly associated with Ee of the BPD infants in our study. Pulmonary status was not associated with other components of the energy balance, such as faecal energy loss and energy stored. It should be noted that the BPD infants had very different oxygen requirements, but that this patient group was

very homogeneous with respect to gender, gestational age, post-conceptual age, and postnatal age. In the BPD group, the frequency of respiration alone explained 82% of the variance in Ee. In the four BPD patients with elevated RR total daily energy expenditure was 25% increased over control values. In contrast, infants with BPD who demonstrated no tachypnoea had a normal Ee (Fig. 1). Physical activity was not associated with Ee, which is in agreement with previous results reported by Yeh and co-workers [21]. Our results support the hypothesis of Kurzner et al. [12] that an increase in mechanical work of breathing (and associated phenomena such as sympatic activity) results in extra energy expenditure in BPD infants. Kurzner et al. [12] found significantly lower lung compliance and higher RR and minute ventilation in BPD infants with growth retardation in comparison with BPD infants without growth failure (no control group of infants without pulmonary disease was studied). Reduced lung compliance may cause increased work of the breathing muscles in BPD infants. Inefficient gas exchange and increased dead space at the level of the alveoli may result in an increased minute ventilation. Increases in ventilation (and RR) and energy cost per breath could result in a disproportional increase of mechanical work of breathing in BPD infants. Furthermore, excessive work of breathing, increased Ee, and elevated RR could be associated, and mutually enhancing, phenomena. However, from the present study no inferences on causality can be made and other explanations for the higher Ee in infants with BPD, such as increased mechanical work by the heart or hormonal disturbances, cannot be excluded.

The association between RR and Ee observed in our study could be of value for the nutritional care of BPD patients of comparable post-conceptual and postnatal age. For practical purposes, the regression equation in the patient group could be simplified to estimate the extra energy required over the baseline in controls. Taking into account 5% faecal energy loss, it can be estimated from the regression coefficient that for a RR over 50 breaths/min, BPD infants require an additional energy intake of 7.5 kcal/kg per day for every additional 10 breaths / min.

Given the concern about growth failure in BPD, it is of interest that the BPD infants in our study were receiving as much energy and gained weight at the same rate as the controls. However, skeletal growth velocity was significantly reduced in BPD infants compared to controls (1.9 vs 3.5 mm/m/day, $P < 0.05$). A similar trend was seen for all three skeletal parameters. Accurate measurements of skeletal growth velocity in young infants are very difficult and our measurements could have been affected by observer bias. Our results suggest that a possible effect on skeletal growth retardation in BPD infants is not mediated by disturbances in energy and protein balance. Although no inferences on relations with other factors can be made from our study, it should be noted that there is growing concern about the possible detrimental effects of corticosteroids on protein metabolism and skeletal growth retardation in these patients with BPD [10, 23–25].

In conclusion, this doubly labelled water study further substantiates the evidence from previous studies that energy expenditure in patients with severe BPD is increased. Present respiratory status, and in particular the infant's respiratory frequency, appears to be strongly associated with total energy expenditure in BPD infants. This finding could be of practical value for the nutritional management of BPD infants with severe lung disease.

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